RECIPIENTS CLINICAL AND MICROBIOLOGICAL

PROFILE RISK FACTORS AND OUTCOME

Dissertation submitted in partial fulfillment of
the requirements for the degree of

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CERTIFICATE

This is to certify that this Dissertation entitled "**URINARY TRACT INFECTION IN RENAL TRANSPLANT RECIPIENTS- CLINICAL AND MICROBIOLOGICAL PROFILE AND RISK FACTORS AND OUTCOME**" is the bonafide original work of **Dr.M.SEENIVASAN**, in partial fulfillment of the requirement for D M., (Nephrology) examination of the Tamilnadu Dr.M.G.R Medical University will be held in August 2013.

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DECLARATION

I, Dr.M.SEENIVASAN, solemnly declare that the dissertation titled "**URINARY TRACT INFECTION IN RENAL TRANSPLANT RECIPIENTS CLINICAL AND MICROBIOLOGICAL PROFILE RISK FACTORS AND OUTCOME**" is the bonafide work done by me at Department of Nephrology, Madras Medical College under the expert guidance and supervision of Dr.N.GOPALAKRISHNAN D.M ,FRCP, Professor of Nephrology,Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of D.M. Degree (Branch III) in Nephrology.

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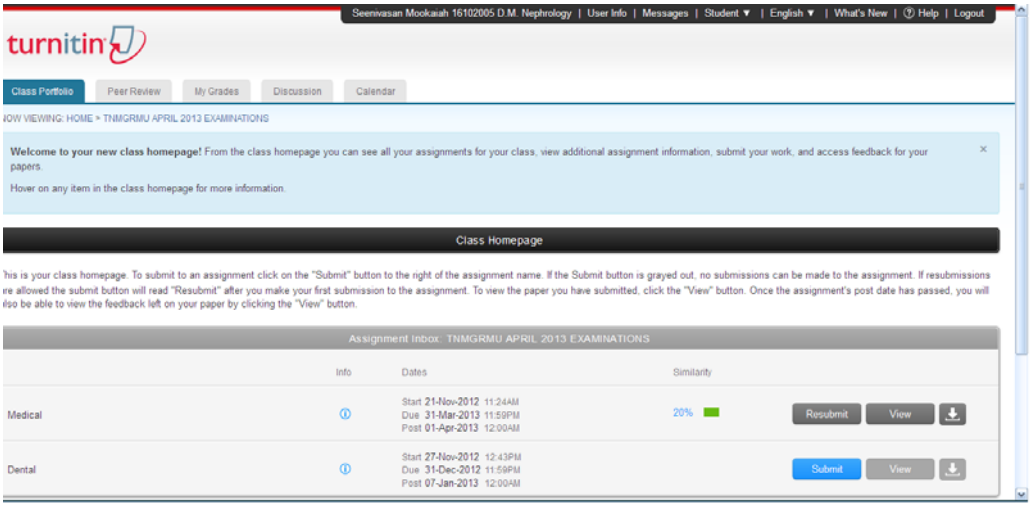
CONTENTS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Introduction Renal transplantation has a better quality of life and improved overall survival when compared to dialysis as a modality of management of end stage renal disease patients. When compared to patients staying on transplant waiting list, renal transplantation is associated with lower risk of mortality, in patients with diabetes, with different age group and in different ethnicity. Renal transplant outcome has improved over the past few decades, as a result of development of new immunosuppressive drugs. The introduction of drugs such as mycophenolate mofetil and Tacrolimus has decreased the incidence of acute rejection episodes. The reduction in acute rejection episodes has improved...

INTRODUCTION

Renal transplantation has a better quality of life and improved overall survival when compared to dialysis as a modality of management of end stage renal disease patients. When compared to patients staying on transplant waiting list, renal transplantation is associated with lower risk of mortality, in patients with diabetes, with different age group and in different ethnicity. Renal transplant outcome has improved over the past few decades, as a result of development of new immunosuppressive drugs. The introduction of drugs such as mycophenolate mofetil and Tacrolimus has decreased the incidence of acute rejection episodes. The reduction in acute rejection episodes has improved the short-term renal survival. In spite of advances in prophylaxis and treatment, infection remains the major cause of morbidity and mortality in patients with renal transplant. Urinary tract infection (UTI) is a common bacterial infection in renal transplant recipient[10]. The majority of infections occur in the first year following transplantation. UTI can worsen the graft and patient survival, may be associated with increased morbidity and mortality risk in renal transplant recipient. A significant percent of patients may develop acute pyelonephritis, which is a risk factor for graft deterioration.

AIM

1. To study the clinical and microbiological profile of urinary tract infection in renal transplant recipients.

2. To study the risk factors for urinary tract infection in renal transplant recipients.

3. To study the effect of urinary tract infection on graft function and long term graft survival.

MATERIALS AND METHODS

Study design- prospective observational study

Study population

Patients attending renal transplant clinic and those admitted in renal transplant ward, Department of Nephrology, Madras Medical College, from July 2011 to December 2012, with fever or urinary symptoms in the form of dysuria, frequency, urgency suprapubic pain or pain over graft, or fever of unknown origin.

Exclusion criteria

Age of the patient less than 16 years

Patients who underwent complex urological surgery like illeal conduit in the pre transplant period.

Evaluation

Clinical details of the patient were collected including age, sex, live or deceased donor, month and year of transplantation, immunosuppressive medication, any induction therapy, any delayed graft function, any rejection episodes, any cytomegalovirus infection, history of hepatitis C sero status, history of diabetes mellitus, previous episodes of urinary tract infection, history

of allograft biopsy, calcineurin inhibitor drug levels and antibiotic prophylaxis of urinary tract infection.

History of duration of bladder catheterization and history of any stenting intra operatively and if positive when stent was removed was noted.

History of present problem including fever duration, intensity and character, vomiting ,loose stools, urinary symptoms like dysuria, frequency, hematuria and Oliguria, and urine output both, before start of the illness and after the start of the illness were noted.

All patients underwent

Urine analysis

Complete hemogram

Blood urea, serum creatinine, serum electrolytes

Serum bilirubin, serum albumin, globulin and alkaline phosphatase

Urine gram stain and culture including fungal

Ultrasonogram abdomen including kidney, ureter and bladder

Blood culture and sensitivity for enteric and non enteric organism

Arterial blood gas analysis in those with sepsis

When complication was suspected, selected patient underwent CT abdomen. Those with recurrent urinary tract infection underwent uroflometry and when obstruction was suspected ascending urethrogram. Hepatitis C virus screening, those with leukopenia during evaluation, cytomegalovirus screening was done

Urine was collected in a sterile manner to avoid contamination of periurethral flora, in the male by retracting the prepuce and in the female by separating the labia majora after washing the external genitalia.

The clean catch mid stream of urine collected with above precaution should be sent to the laboratory immediately and plated on the MacConkey agar and Blood agar within 1 hour. If time delay is expected between collection and plating the urine is stored in the refrigerator upto 12hours.

Statistical analysis

All data are expressed as mean± standard deviation. Differences in categorical variables were compared using fisher's exact test. The variables were compared using student t test. The difference was considered to be significant if the P-value was <0.05. Data was analyzed using SPSS software.

REVIEW OF LITERATURE

RISK FACTORS FOR URINARY TRACT INFECTION (UTI)

The incidence of UTI in immunosuppressed solid organ transplant recipients other than renal transplant recipients is not increased, when compared to non immunosuppressed individual. The incidence of UTI is increased in simultaneous kidney-pancreas transplantation with drainage of exocrine secretion into the bladder.

Ageing

Female recipient, pre transplant UTI

Induction agent, Azathioprine based regimen

Technical complication, allograft trauma (double renal transplant)

Post operative bladder catheterization, ureteral stent placement

Structural abnormalities like reflux nephropathy (native kidney), stone disease, diabetes

Neurogenic bladder

Deceased donor and malnutrition

Basic disease- Glomerulonephritis as a cause of ESRD[62]

Net state of immunosuppression

One of the determinants of infection risk after transplant is net state of immunosuppression. The risk of infection increases for several months after high dose steroid for rejection. Particularly immunomodulatory viruses like EBV, CMV, and BKV infection are increased. There is also increased risk for bacterial, fungal and parasitic infection after rejection therapy. There is a need for surveillance for bacterial and fungal infection post anti-rejection therapy.

1. Immunosuppressive therapy (current and past)
2. Underlying immune deficiency (Systemic lupus erythematosis)
3. Prior therapies (chemotherapy, antimicrobials)
4. Lymphopenia, Neutropenia
5. Mucocutaneous barrier integrity (lines, catheters, drains)
6. Viral coinfection (CMV,HBV, HCV)

DEFINITIONS

Cystitis is defined by clinical manifestation of dysuria, frequency and urgency and by the presence of bacteriuria in the absence of symptoms of pyelonephritis.

Pyelonephritis is defined by simultaneous presence of bacteriuria and fever with any one of four features

Pain over the graft

Lumbar pain

Chills

Lower urinary symptoms- dysuria, frequency, urgency

Reinfection is defined by a new episode of infection

1. with the same organism, with different antibiotic sensitivity pattern

2. Isolation of the organism other than one that caused the previous episode

Recurrence is defined as more than two (≥3) UTI in a twelve months period.

Relapse is defined as isolation of same bacteria that caused the preceding infection, with the same sensitivity pattern, in a culture obtained ≥ 2weeks after completing the previous treatment.

MICROBIOLOGY

Gram negative organism - E. coli is the most common organism isolated in post transplant UTI. Other organisms include proteus, klebsiella, pseudomonas, serratia, citrobacter, acinetobacter and Corynebacterium urealyticum.

Gram positive organism – coagulase-negative staphylococcus, enterococcus species

HOST DEFENCE

Symptomatic infection caused by uropathogenic strain of microorganism induces a strong innate immune response, while a limited immune response is induced by strains, causing asymptomatic bacteriuria. Bacterial adherence to uroepithelial cells and direct stimulation of epithelial cells by lipopolysaccharide causes the cytokine elaboration like IL-6 and IL-8.

The cytokines cause migration of neutrophils and other inflammatory cells to the bladder and kidney, particularly IL-8 released at the mucosal site recruit polymorphonuclear leukocytes. Urine IL-6 levels correlate with the severity of infection with higher levels occurring in patients with pyelonephritis. The polymorphonuclear leukocytes infiltration developing in renal tissue in pyelonephritis limits bacterial spread, but also causes tissue damage and renal scaring.

Humoral immunity

There is an IgM antibody response to first episode of infection the upper UTI particularly against the surface antigens of E. Coli including O antigens, type 1 and P fimbriae. In subsequent episodes antibody response is IgG with elevated levels correlating with severe renal infection. There are also increased urinary levels of IgG and IgA.

Cell mediated immunity has a less role in the host defence mechanism against urinary infection, as evidence by low susceptibility to UTI in HIV infected women with very low CD4 counts[15].

AGENT FACTOR

E.coli colonise colon of new born soon after birth. Some of these strains colonise periurethral area and enter bladder. Majority of infections are caused by Uropathogenic E.coli(UPEC).They possess a variety of virulence factors like polysaccharide capsule, adhesins, siderophores and cytotoxins including hemolysin, cytotoxic necrotising factor, Secreted Autotrasporter Toxin. Among the 4 main phylogenitic groups, B2 &D groups cause more infection than A &B1[63].

Pathogenicity associated islands (PAIs) are virulence factor rich clusters of DNA .These mobile genetic elements contribute to the emergence of pathogenic strains from commensal group.

Molecular interactions between adhesins on bacterial surface and epithelial cell receptors favour tropism. Type I fimbria bind to mannose containing glycoprotein via Fim H adhesin. UPEC have 20 times increased affinity to uroepithelial cells[63]. New adhesin P fimbriae is encoded with in chromosomal PAIs. The receptor for P fimbriae is gal-gal disaccharide, a glycolipid found in renal epithelium. Other fimbrial factors are Dr Adhesin family, FIC fimbria and S fimbriae family.

Prophylaxis

Antimicrobial prophylaxis has decreased the incidence and severity of infection in the posttransplant period[55]. Three general preventive strategies are used: (1) vaccination, (2) preemptive or presymptomatic therapy and (3) universal prophylaxis including surgical prophylaxis. Universal prophylaxis involves giving antimicrobial therapy to all 'at-risk' patients for a defined time period. The use of trimethoprim-sulphamethoxazole from three months to life time is used for prophylaxis of urinary tract infection and PCP pneumonia[55]. The TMP-SMX also covers *Toxoplasma gondii*, *Isospora belli*, *Cyclospora cayetanensis*, many *Nocardia* and *Listeria* species, in addition to common urinary microbes. In the absence of allergy or interstitial nephritis, low dose TMP-SMX should be continued. In the one to 6 months period TMP-SMX is able to prevent opportunistic infection and urinary infection when the peak effect of immunosuppression is noticed. Those patients who are not tolerating TMP-SMX, quinolones can be used for preventing urinary tract infection.

NOSOCOMIAL INFECTION

Nosocomial infection, is an infection, one acquired by a patient during a hospital visit or one developing among hospital staffs, whose development is favoured by a hospital environment,. Such infections include fungal and bacterial infections and are aggravated by the reduced resistance of individual patients. Nosocomial infections include fungal and bacterial infections.

Nosocomial infections are aggravated by the reduced resistance of individual patients.

Nosocomial infections can cause severe pneumonia and infections of the bloodstream, urinary tract and other parts of the body. Many types of antibiotic resistance are spreading to Gram-negative bacteria that can infect people outside the hospital. The nosocomial infections more commonly occurs in the urinary tract, surgical site and lungs. One third of nosocomial infections are considered preventable.

Nosocomial bacteria include MRSA (resistant strain of *S. aureus*), member of Gram-positive bacteria and *Acinetobacter* (*A. baumannii*), which is Gram-negative and the drug-resistant, Gram-negative *Klebsiella pneumoniae*. Few effective drugs are available for acinetobacter and the bacteria is evolving and becoming immune to existing antibiotics, in many cases they are sensitive to polymyxin group of drugs only. More than 20% of Klebsiella pneumonia are now resistant to virtually all modern antibiotics. The gram-negative bacteria can cause severe pneumonia and infections of the urinary tract, bloodstream, and other parts of the body. Most common site of involvement is urinary tract, followed by lung and surgical site. Nosocomial infections prolong the hospital stay by four to five additional days. The nosocomial infections threaten only hospitalized patients whose immune systems are weak. The bacteria can

survive for a longer time on surfaces in the hospital and enter the body through catheters wounds, or ventilators

Main routes of transmission are direct contact, through droplet, airborne, common vehicle and vector borne

Route	Description
Contact transmission	The most important and frequent mode of transmission of nosocomial infections is by direct contact.
Common vehicle transmission	This applies to microorganisms transmitted by contaminated items to the host, such as food, water, medications, devices, and equipment.
Vector borne transmission	This occurs when vectors such as mosquitoes, flies and rats transmit microorganisms.

Contact transmission is divided into two subgroups: direct-contact transmission and indirect-contact transmission.

Factors predisposing to infection

1. Poor health- General risks for nosocomial infection are advanced age with immunodeficiency and in renal transplant patients with pretransplant malnutrition.

2.Invasive devices- Patients are colonized with organisms while in hospital and on invasive devices, for instance catheters, surgical drains,

intubation tubes, and tracheostomy tubes, all bypass the body's natural lines of defence against pathogens and provide an easy entry for microbes.

3. Patient therapy- Antimicrobial therapy while removing competitive flora, leaves only resistant organisms, recurrent blood transfusion and treatment with antacid and immunosuppression treatment undermine the body's defences.

CATHETER ASSOCIATED INFECTION

Catheter associated infection is defined as the infection occurring in an individual whose urinary tract is currently catheterised or who has been catheterized within the previous 48 hours. The incidence of bacteriuria in those with indwelling bladder catheterization is 3% to 8% per day. Risk factors for catheter associated UTI include female gender, microbial colonization of drainage bag, diabetes mellitus, positive urethral meatal culture and not receiving systemic antimicrobial therapy. Most catheters are latex based which is associated with inflammation, urethritis, penile discomfort and stricture formation.

Organisms causing catheter associated UTI are E. coli, proteus, klebsiella, pseudomonas, enterococcus, coagulase-negative staphylococcus, serratia citrobater and enterobacter. E. coli is the most common organism isolated in about one-third of patients.

Pathogenesis- Urinary catheter is an important predisposing factor for nosocomial UTI. At the time of insertion the catheter introduces an inoculum of bacteria into the bladder. After catheterization residual urine in the bladder is increased due to pooling below the catheter bulb.

Portal of entry of microorganism
- External surface of the catheter- 66%
- Via the lumen of the catheter - 34%

Biofilm formation

Bacteria attaches to the catheter by using adhesins, to the host cell receptors on the catheter surface. Then, they change phenotypically and produce exopolysaccharides which cover and protect replicating bacteria, forming microcolonies, and ultimately forming mature biofilms. Biofilms develop on both inner and outer surface of the urinary catheter. There is exchange of genetic material among organism within the biofilm, which facilitates the spread of antimicrobial resistance genes. In catheters with biofilm, bacteria isolated in urine obtained through the catheter may not reflect the bacteria in the bladder urine causing UTI.

Specimen collection

A urine specimen for culture should be obtained prior to starting antimicrobial therapy for suspected catheter associated UTI, because of the wide spectrum of the possible infecting organism. Specimens for culture are

obtained by sampling through the catheter port or if the port is not present, puncturing catheter tubing with syringe and needle. Culture specimen should not be collected from the drainage bag. In patients with long term catheterisation, urine specimen should be obtained after the catheter has been replaced.

Diagnosis

Symptoms and signs in patients with indwelling bladder catheterization including new onset or worsening fever, rigors, altered mental status, malaise or lethargy with no other identified cause; acute hematuria; pelvic pain; pain and tenderness over allograft, along with ≥1000 cfu/ml of bacteria in a single catheter urine specimen indicates catheter associated UTI. In catheterised patients absence of pyuria suggests a diagnosis other than catheter associated UTI. Pyuria in the absence of bacteriuria is not diagnostic of catheter associated UTI. Unpleasant odour of urine does not indicate bacteriuria in all patients. Like-wise not all patients with UTI have unpleasant odour.

In patients on clean intermittent catheterization ≥ 100 cfu/ml in a catheter urine specimen is significant.

Prevention

Indwelling catheters should be inserted using aseptic technique and sterile equipment

A closed catheter drainage system with port in the distal part for needle aspiration of urine should be used to reduce catheter associated UTI.

Systemic antimicrobial therapy before insertireduces catheter associated UTI in short term, but should not be given routinely, because of the chance of antimicrobial résistance.

The most effective way to reduce catheter associated UTI is to remove the catheter promptly when it is no longer needed.

Treatment

General measures- antimicrobial resistance is increasing, so antimicrobial susceptibility testing is to be done in all bacterial isolates. Antimicrobial therapy is to be administered against the specific pathogen identified according to the culture result. Initial therapy in critically ill patient should be broad spectrum which is to be narrowed after 24 to 48 hours, depending on the culture report. Nephrotoxic drugs like aminoglycosides or amphotericin to be avoided, if equally effective alternative agents are available. When the organism is multidrug resistant one like carbapenem resistant klebsiella pneumonia, nephrotoxic drug like intravenous colistin can be used.

Drug level should be measured when available like vancomycin, aminoglycosides, voriconazole. Reduction of immunosuppression during episodes of infection will help in resolution of infection- including decrease in mycophenolate mofetil or azathioprine dose or targeting a lower level of

calcineurin inhibitor. For those with recurrent infection, there may be a need for long term reduction in immunosuppression if it can be done without inducing rejection. For patients with neutropenia with fever or symptoms or signs of infection, granulocyte colony-stimulating factor is administered to increase the neutrophil count. There is no increased incidence of rejection with granulocyte colony-stimulating factor. Drugs that can cause leukopenia should be discontinued temporarily when there are symptoms or signs of infection in leukopenic transplant recipient like Azathioprine, MMF, and valgancyclovir.

When the patient has prompt resolution of symptoms, the duration of therapy for catheter associated UTI is seven days. When the patient has delayed response the duration of therapy is 10 to 14 days irrespective of whether the catheter is removed or not.

URETERAL STENTING

Vesicoureteral anastomosis initially was done by transvesical approach (Lead better politano technique). Now the technique is end-to-side extravesical implantation of the ureter into the anterior wall of the bladder, by modified Lich-gregoire technique[29]. The anastomosis was made between the spatulated distal donor ureter and a small bladder mucosal nick.

Double-J stent has a straight tube with anchoring J loops at the end. Prophylactic stenting of the ureter is being done to avoid major urological complication originating from vesicoureteral junction anastomosis. The

complications of anastomosis occur during the early post transplant period mostly in the first three months. The complications include obstruction, urinary leak, necrosis, and stenosis and vesicoureteral reflux[30]. The ureteric obstruction can also be caused by intraluminal obstruction, such as calculi, blood clots, or extraluminal compression of blood and lymphatic fluid[36, 37]. The urological complication arises as a result of distal transplant ureteral ischemia or due to surgical factors like ureteroneocystostomy techniques and poor graft harvesting. These complications cause delayed graft function, increased morbidity and may cause graft or patient loss[28]. Stenting is preferred by most transplant surgeons, when the healing process is either expected to be delayed or there is an increased risk of urine leak after transplantation

INDICATION FOR DJ STENTING

1. Dry anastomosis: No urine output after implantation of the graft

2. Graft kidneys from deceased donors

3. Prolonged ischemia time like in deceased donor[40]

4. Abnormal bladder- small bladder, neurogenic bladder, irradiated bladder and urethral valve [34]

5. Those with comorbidities like multiple abdominal surgeries, obesity, and previous peritonitis where wound healing is expected to be delayed

6. Precarious ureteric blood supply- Extensive mobilization of donor ureter, double ureter, shortened or injured ureter, or accidental dissection of the golden triangle.

Benefits of stenting are simplifying the creation of water tight anastomosis and reduced incidence of anatomical kinking.

Complications of stenting- are stent migration, irritative bladder symptoms like post operative pain and stone formation in the graft kidney after transplantation, persistent hematuria, encrustation, breakage, complication during removal, forgotten stents, erosion of lumen and importantly post operative urinary tract infection[25]. Stent can also exacerbate long-term stricturing of the ureter[33].

The incidence of UTI is increased not only during stenting period, but also after removal of the stents. Stenting can convert what may be a simple urinary tract infection to complicated pyelonephritis, and can act as a focus for bacterial persistence[38]. In those who has stenting, there is higher relative risk of BK virus allograft nephropathy[39].

In normal urological practice stenting is advised, since ureteroneocystostomy is done on abnormal ureters. Transplantation is a procedure where normal ureter is involved in ureteroneocystostomy to a normal bladder. Stenting cannot be a substitute for a carefully done

ureteroneocystostomy, even when ureter needs to be anastomosed to abnormal bladder.

Stent can be avoided by tension-free anastomosis and proper care is taken for maintaining the ureteric vascularity[31]. The preservation of the ureteric blood supply as maintained by (1) nondissection technique in the golden triangle, (2) preservation of lower pole graft vessels during dissection and anastomosis, and (3) avoiding dissection close to the periureteric adventitia and there by maintaining the ureteric blood supply is essential to avoid transplant ureteric ischemia. Stenting should be restricted to difficult ureterovesical anastomosis and unfavourable anatomy. The duration of stenting may be limited to 3 or 4 weeks to avoid the complication due to stenting[33].

SUPPRESSIVE ANTIMICROBIAL THERAPY

Suppressive antimicrobial therapy is indicated in patients with frequent and recurrent symptomatic infection

With underlying genitourinary abnormality that cannot be corrected

Renal transplant recipient

Renal failure or those with ureteric stents

Stent coated with biofilm contains high concentration of urease producing microorganisms particularly proteus species, pseudomonas aeruginosa, klebsiella pneumonia and providencia species. These organisms

have the capacity to hydrolyse the urea in the urine to free ammonia, causing elevation in local pH facilitating precipitation of minerals, which can block urine flow. The organisms growing in biofilms are protected from both antimicrobials and host defences. Ultimately relapse of infection occurs in post transplant patients.

Suppressive antimicrobial therapy involves initial period of full dose therapy still negative culture, followed by reduced dose for 12 to twenty four weeks. Norfloxacin is the commonly used drug for suppressive prophylaxis.

ASYMPTOMATIC BACTERIURIA

Definition

Women - Asymptomatic bacteriuria is defined as isolation of the same organism $>10^5$ colony-forming units/ml on two consecutive voided specimens.

Men – asymptomatic bacteriuria is defined as isolation of one bacterial species $>10^5$ colony-forming units/ml of clean-catch voided urine specimen, on a single occasion, without any symptoms of urinary tract infection.

Systemic screening and treatment of asymptomatic bacteriuria in patients who have undergone transurethral resection of prostate and in pregnant women have been associated with reduction in pyelonephritis. In diabetic women treatment of asymptomatic bacteriuria is not useful in preventing pyelonephritis or diabetic nephropathy.

The incidence of pyelonephritis was more frequent in patients with asymptomatic bacteriuria[16]. Pyelonephritis episodes were associated with rejection in renal transplant recipients. Repeated episodes of asymptomatic bacteriuria, even with systemic treatment are an independent risk factor for the occurrence of pyelonephritis.

Treatment

Systemic treatment of asymptomatic bacteriuria may reduce the incidence of pyelonephritis[50]. The antibiotics recommended for treatment of asymptomatic bacteriuria are

Ciprofloxacin 250 mg twice daily for 3 days

Amoxicillin-clavulanate 625 mg 8th hourly for 7 days

Cefuroxime 250 mg 12th hourly for 7 days

FUNGAL UTI

Fungal infections primarily affect the bladder and kidneys. The most common cause is candida species, which are normal commensals in humans. The candida species causing UTI are Candida albicans, Candida glabrata, Candida tropicalis and Candida parapsilosis. The majority of these infections occur within the first two months after transplantation.

Risk factors

1. Prior antibiotic therapy
2. Urinary tract devices
3. Diabetes
4. Urinary tract structural abnormalities
5. Maintenance Tacrolimus and allograft rejection

Candida cystitis

Usually occurs with presence of urinary catheters and after bacteriuria and antibiotic therapy. Candidal and bacterial infection usually occur simultaneously[51].

Symptoms

Most patients with candiduria are asymptomatic. They may present with dysuria, frequency, urgency and suprapubic pain. Hematuria is common and may present with pneumaturia due to emphysematous cystitis or symptoms of urethral obstruction due to fungal balls in the bladder.

Diagnosis

Ccandida UTI is diagnosed by urine culture. Differentiating candida colonisation from infection is difficult. When candiduria is associated with pyuria suggesting bladder inflammation, infection can be diagnosed[52].

Candida pyelonephritis

Uusually occurs through hematogenous seeding from the gastrointestinal tract. Ascending infection can also occur in patients with

permanent indwelling bladder catheter and ureteral stents. The major source of candidemia in immunosuppressed hospitalised patients is an indwelling intravascular catheter.

Symptoms and signs

Due to hematogenous spread most patients lack renal symptoms. They may present with antibiotic resistant fever, unexplained graft dysfunction or candiduria. They frequently have hematuria and urinary obstruction due to fungal ball in the pelvis or ureter. Some patients may have loin pain, fever, hypertension due to papillary necrosis or intrarenal or perinephric abscesses. They may present with manifestation in other sites like liver, spleen, skin, eyes or CNS.

Diagnosis

Identifying the species of candida by culture is necessary and antifungal susceptibility to be done in urine culture. Blood cultures for candida are often negative. Fever with passage of fungus balls suggests renal infection. Severe renal failure is unusual unless there is post renal obstruction. Imaging of transplant kidney to rule out collecting system abscess or presence of fungus ball is recommended.

Treatment

Systemic prophylaxis of fungal infection is generally not required.

Fungal colonization of catheters does not require treatment.

Candiduria should be treated in the following situations:

1. Asymptomatic patients: with renal allograft and neutropenic patients.

   IDSA recommend treatment of asymptomatic candiduria with Fluconazole 200 mg orally per day for 7 to 14 days or I.V. amphotericin B, 0.3 to 1 mg/kg/day for 1 to 7 days. The ecchinocandins achieve low urinary concentration not recommended for fungal urinary tract infection. Intravesical irrigation of amphotericin B is not useful.

2. Symptomatic patients

3. Urinary catheters and stents should be removed if possible

Most common antifungal agents used for the treatment of candidemia are fluconazole, amphotericin B and caspofungin. Fluconazole is the only azole concentrated in the urine, so has important role in the treatment of UTI.

Many Candida glabrata strains are resistant to fluconazole. The Infectious Disease Society of America recommends to avoid the use of fluconazole for the treatment of C. glabrata[13]. Amphotericin B remains the drug of choice, though caspofungin is preferred due to its better safety profile. Oral

or intravenous voriconazole has been recommended for disseminated infections caused by candida species and in patients refractory to other antifungal therapy[14].

Duration of therapy- two weeks of therapy after cultures become negative is advised.

Drug interactions and toxicities of anti-fungal agents

Therapeutic drug level monitoring of the primary immunosuppressant must be done frequently and dose adjusted to achieve the desired level of the drug, both when initiating and discontinuing anti-infective therapy. As interaction with ketoconazole is potent, there is a need for reducing the cyclosporine dose by 80%.

Anti fungal agent	**Drug interactions or toxicities**	**Additional information**
Amphotericin B	Enhanced nephrotoxicity	For invasive fungal infection, liposomal formulations preferred to reduce risk of nephrotoxicity
Clotrimazole (topical)	Increased level of Tacrolimus via Cytochrome P4503A4 inhibition in the gut	Dose adjustment often needed
Azole antifungals	Increased levels of Tacrolimus, cyclosporine, everolimus and sirolimus via	Empiric dose adjustment of immunosuppressant is recommended when

	Cytochrome P4503A4 inhibition	initiating azole therapy

Other invasive fungal infections- may infect the kidneys as part of systemic or disseminated fungal infection[12]. They are Cryptococcus neoformans, Aspergillosis, and endemic mycosis like Histoplasma capsulatum, Blastomyces dermatitides, Coccidiodes immitis. Infections typically occur in the mid to late post transplant period, although some occur within two months of transplant.

VIRAL UTI

Adenovirus- is a double stranded DNA virus, usually associated with mild, self limiting upper respiratory tract syndromes in immunocompetent children. This is followed by asymptomatic latent infection of lymphoid tissue[41].

Major syndromes caused by adenovirus are acute respiratory disease, acute hemorrhagic cystitis (serotypes 11 and 21), gastroenteritis, pharyngoconjunctiva l fever and epidemic keratoconjunctivitis.

Risk factors in transplant recipient

T-cell depleting agents, lymphopenia, prolonged neutropenia, young age and graft versus host disease.

Clinical features

In immunocompromised adenovirus infection present with disseminated infection including hemorrhagic cystitis, nephritis, pneumonitis, hepatitis and gastroenteritis, present as diarrhoea with dehydration, dyspnoea, dry cough, reticulonodular pulmonary infiltrates and elevated transaminases or fever of unknown origin[42].

Adenovirus **cystitis** present with hematuria for less than 3 days, without fever. **Nephritis** present with flank pain and fever.

Diagnosis

Antigen detection by indirect immunofluorescence assays in tissue specimens.

Polymerase chain reaction used to identify adenovirus on various specimens including urine blood and sino-nasal and lung tissue[43].

Renal- Urine analysis, urine culture both viral and bacterial and ultrasonogram to demonstrate enlarged kidneys. Other causes to be ruled out if hemorrhagic cystitis does not resolve within 5 days.

Renal biopsy

Shows non-specific lymphocyte infiltration. Tubular epithelium shows viral intranuclear and intracytoplasmic inclusions (smudge cells) with positive immunohistochemical staining specific for adenovirus.

Treatment

1. Reduction of immunosuppression
2. Intravenous immunoglobulin 0.5 gm/kg/dose for four doses
3. Cidofovir 0.5 mg/kg single dose[44]

It is a cytosine analogue that inhibits viral DNA polymerase. Cidofovir is highly concentrated in renal tissue and urine, so lower doses might be adequate to treat renal or bladder involvement. Even treatment of dialysis dependent renal failure due to adenovirus can recover following cidofovir therapy[45].

Other drugs useful are ribavirin, ganciclovir, and vidarabine.

POLYOMA VIRUS-ASSOCIATED NEPHROPATHY

Polyoma virus was first isolated from a kidney transplant recipient with a ureteric stricture. After kidney transplant, 10% to 60% of patients excrete the virus in their urine. The viruria in polyoma virus is asymptomatic or associated with only transient graft dysfunction. BK virus nephropathy has profound effect in allograft survival and quality of life. Roughly 30 to 60 % of patients with polyoma virus nephropathy develop graft failure.

Primary infection with BK virus occurs during early childhood. The common mode of transmission is respiratory secretion. The seroprevalence in adults is more than 70%. BK virus latent infection is established in renal tubular epithelial cells. The virus may be in the episomal form or incorporated into the host cell genome. During latent infection few viral transcriptions occur, so it evades from host immunity during latency. BK virus remains latent in endothelial cells, connective tissue cells, renal tubular cells, blood leukocytes, ependymal cells of brain and astrocytes. Asymptomatic viruria occurs in 5% of healthy individuals. Viruria is common in mild immunodeficiency state like pregnancy, diabetes and elderly. The prevalence of viruria may increase with immune dysfunction to reach more than 60%. The prevalence rate of polyomavirus nephropathy varies from 1% to 10% in renal transplant recipients.

Mode of spread

a. The donor kidney itself
b. The possibility of fecal/oral transmission recently has been raised by the demonstration of viral DNA in urban sewage
c. Urine
d. Nasopharyngeal aspirate obtained from infants with respiratory infections
e. Sexual contact particularly for reactivation
f. Transplacental route

Risk factors

1. BK virus–seronegative recipients.
2. BK virus–seropositive donors.
3. Intense triple-drug immunosuppression with agents including calcineurin inhibitors particularly tacrolimus[3]
4. Renal transplant
5. HLA antigen mismatches
6. Rejection and antirejection treatment
7. Low number BK virus–specific interferon-8–producing T cells[2]

Pathogenesis

Polyoma virus entry into host cells depends on caveola-mediated pathway. Factors contributing to nephropathy are defective surveillance by T cell, absence of viral specific humoral immunity and alloimmunization[5].

It was found that patients with polyoma virus nephropathy had reduced number of BKV-specific IF-¼-secreting lymphocytes. When the immunosuppression is reduced there is increase in the IF-¼-secreting lymphocytes. After full resolution of infection there is 4 fold rise in IF-¼ levels.

Viral genome contains epitopes within large T cell antigen, and VP1 gene product, which are responsible for lymphocytes recognition. Site within viral T cell antigen particularly P53 binding region of large T cell antigen,

promoted CD8+ T cell response. In the same way two regions of viral capsid protein VP1 were recognized by cytotoxic T lymphocytes. It was observed that viral agnoprotein levels are increased after infection, which would contain epitopes for T cell stimulation.

The role of humoral immunity is suggested by the fact, that recipient of a kidney from a seropositive donor was more likely to develop polyoma viremia. Recipient seronegativity was a significant risk factor for polyoma viremia.

Polyoma virus nephropathy does not occur in liver and heart transplantation. There is more incidence of polyoma virus nephropathy when there is a higher degree of HLA mismatches. Polyoma virus nephropathy is specific to renal allograft recipient. It indicates subclinical alloactivation in graft may trigger nephropathy.

Type of immunosuppressive regimen

BK virus nephropathy is more common with the use of tacrolimus when compared to cyclosporine and mycophenolate mofetil when compared to azathioprine. Immunosuppressive agents containing tacrolimus-MMF combination is the most permissive regimen for BK virus reactivation. Lower incidence of BK virus nephropathy is also associated with steroid avoidance or early steroid withdrawal regimen. BK virus replication has also been associated with higher dose of MMF or tacrolimus. Improvement or stabilization of nephropathy occurs with dose reduction.

Clinical features

Polyoma virus nephropathy occurs within the first post transplant year. Patients are usually asymptomatic and present with unexplained graft dysfunction.

Primary infection-hemorrhagic and non hemorrhagic cystitis, and tubulointerstitial nephritis.

Reactivation- hemorrhagic cystitis or hematuria, tubulointerstitial nephritis and occasionally they present with renal dysfunction secondary to ureteric stricture. Sometimes they present with severe systemic symptoms with multi organ failure. The cystitis that is common in polyoma virus is late onset and long duration hemorrhagic cystitis. Reactivation in other organ causes

meningoencephalitis, interstitial Pneumonitis, atypical retinitis, renal and urinary tract neoplasm[57].

Diagnosis

Renal biopsy is the gold standard for the diagnosis of polyoma virus-associated nephropathy[4]. There is focal involvement; it is advisable to evaluate at least two cores of renal tissue[59]. The characteristic finding on light microscopy is the intranuclear basophilic viral inclusions in uroepithelial cells.

In early stages viral changes are present with little to no inflammation or tubular atrophy. In late stages viral cytopathic changes are associated with varying degrees of inflammation, tubular atrophy, and fibrosis. In latter stage cytopathic changes are less apparent, in the back ground of interstitial fibrosis, tubular atrophy and chronic inflammatory infiltrate.

Other morphologic features include glomerular crescents, transplant glomerulopathy, tubular micro calcification, and abundant plasma cell infiltration.

Simian virus 40 immunoperoxidase staining is useful in differentiating lesions mimicking acute cellular rejection with lymphocytic infiltration. Tubular basement membrane staining for C4d staining occurs in some and is associated with more severe disease. Higher proportion of CD20+ positive cells in the kidney biopsy well correlated with polyoma virus nephropathy.

Urine

Decoy cells originate from infected renal tubular cells altered by viral inclusion, are identified in polyoma virus nephropathy[6]. The characteristic feature of BK virus is large homogenous basophilic nuclear inclusions. Decoy cells may also be seen in JC virus and less commonly adenovirus infection. Decoy cell in urine has a sensitivity of 25% for BK viruria[7].

Urine VP1 mRNA indicates active viral infection.

Urine PCR has a sensitivity of 100% for BK viruria[57]. The interval from viruria to viremia is one to three months. The median time from viremia to BK virus nephropathy is 1 to 12 weeks.

Threshold for diagnosis of BK virus nephropathy is plasma viral load > 10^4 copies/ ml, higher viral load is correlated with more severe disease[8]. Nephritis can also occur with BK virus DNA <7000 copies/ml[66].

Treatment

The treatment of BK virus nephropathy is reduction of immunosuppression. The immune reconstitution controls infection after 4 to 12 weeks. Patients who had polyoma virus infection, and inadvertently given pulse corticosteroids, or anti lymphocyte agent for presumed acute rejection have a rapid worsening of graft function.

The **university of Maryland protocol** involves three steps.

Step1- Decrease the dose of MMF by 50% immediately after diagnosis.

Step2- Reduce the trough level of tacrolimus at three months if decoy cells persist.

Step 3- Withdraw MMF at 6 months if there is persistence of decoy cells. If there is no response, reduce the calcineurin inhibitor dose to maintain a target level between 3to5 ng/ml for tacrolimus and 50 to 100 ng/ml for cyclosporine. There is 10 to 15% chance of acute rejection with reduction of immunosuppression[9].

Anti viral therapy

Leflunomide-a pyrimidine analogue immunosuppressant, is also an immunomodulatory drug. It acts by inhibiting mitochondrial enzyme dihydro-orotate dehydrogenase, which acts in the de novo synthesis of the pyrimidine ribonucleotide uridine monophosphate. Leflunomide primarily acts on activated and autoimmune lymphocytes by interfering with their cell cycle progression. The non-lymphoid cells are able to use salvage pathway to make their ribonucliotides, which make them less dependent on de novo synthesis. It has anti-inflammatory effect, in addition to antiproliferative activity.

Leflunomide is metabolized to teriflunomide, after oral absorption, which is responsible for all of the drug's activity in vivo. This metabolite of teriflunomide has anti viral properties, in addition to immunosuppressive properties[58].

Teriflunomide is metabolized in the liver by cytosolic and microsomal enzymes and further excreted in both urine and bile. After oral administration, peak plasma levels of teriflunomide occur between 6 and 12 hours after dosing. Teriflunomide has a long half-life of approximately 2 weeks.

A loading dose of 100 mg for 3 days is administered to reach steady-state levels quickly. When loading dose is not given, the steady-state plasma concentrations would be achieved in two months of dosing. Teriflunomide can be found in human plasma at sufficient levels upto 2 years after termination of therapy. Teriflunomide is not dialysable.

Leflunomide should be started with the simultaneous discontinuation of antiproliferative agent and decreasing the dose of tacrolimus. With this treatment there is reduction in viral load.

Contraindications

Pre-existing pregnancy or women of childbearing potential not using reliable contraceptive methods are an important contraindication. Women should not become pregnant before 2 years after termination of therapy as the

drug is slowly cleared. -Preexisting liver or renal disease -Moderate to severe diseases of the bone marrow or immune system -Severe bacterial, fungal or viral infections like active TB, pneumonia, AIDS or latent HIV

Side effects

The most serious side effect is hepatitis, which can be fulminant, with severe liver necrosis, and liver cirrhosis. The incidence of severe liver damage is as high as 0.5%. The liver damage is typically seen within the first 6 months of therapy and it partially depends on concomitant administration of other hepatotoxic drugs. Risk factors for severe liver damage include history of alcohol abuse, acute heart failure, severe pulmonary disease or liver function disturbance.

Hematological side effecs are myelosuppression with leukopenia, anemia, and/or thrombocytopenia. Infectious side effect includes development of active tuberculosis, PCP, pneumonia, and severe viral or mycobacterial infections, possibly leading to sepsis, death. Anemia or bleeding episodes may cause serious complications.

Interstitial lung disease present as progressive dyspnoea and typical X-ray findings, which may or may not be reversible upon treatment. ILD may lead to permanent disability or death. To slow or reverse the severe side-

effects, rapid removal of toxic metabolite is done by oral cholestyramine or activated charcoal.

Cidofovir is an antiviral drug belonging to nucleoside analogue drug. When there is failure to respond to immunosuppressive dose reduction, cidofovir can be administered.

Dose – The dose recommended for polyoma virus nephropathy is 10 to 20% of the dose needed in CMV infection (0.25 to 1.0 mg/kg). Side effect- cidofovir toxicity mainly involve the kidneys Proteinuria more than 2+ and renal failure occurs in upto 60% of patients receiving a maintenance dose of 5 mg/kg every fortnightly. Cidofovir nephrotoxicity is irreversible. Renal impairment, including cases of acute renal failure resulting in dialysis or contributing to death, can occur with as few as one or two doses of the drug. **Prevention-** Adequate hydration and concomitant administration of probenecid decreases the risk of renal toxicity associated with cidofovir. Proteinuria is an early indicator of cidofovir-associated nephrotoxicity. Before each dose of cidofovir administration, serum creatinine concentrations and urinalysis should be monitored. Patients who had previously received foscarnet are at increased risk of renal toxicity and should be monitored closely. Other effects are neutropenia, anaemia, thrombocytopenia, decreased intraocular pressure, nausea, vomiting, diarrhoea, abdominal pain, pancreatitis, fever, decreased

serum bicarbonate and fanconi's syndrome, hepatitis, hepatic necrosis, dyspnoea and pneumonia.

Fluoroquinolones have anti-BK properties through inhibition of DNA topoisomerase and polyomavirus associated large T-antigen helicase .In vitro analysis has shown that fluoroquinolones - nalidixic acid and oxolinic acid are capable of inhibiting BKV DNA replication. Other fluoroquinolones trovafloxacin, ciprofloxacin, levofloxacin, ofloxacin, and gatifloxacin also have the ability to inhibit viral DNA replication and T-antigen helicase activity of SV40. In permissive monkey cells, fluroquinolone has the ability to inhibit viral replication and block the cytopathic effect of SV40 virus.

The use of a 1-month course of fluoroquinolones immediately after the transplantation was associated with a significant reduction in the incidence of BK viremia.

Prophylaxis – with ciprofloxacin in hematopoietic stem cell transplant recipients, decrease the incidence of BK viruria and significantly reduces the rate of hemorrhagic cystitis.

RESULTS

The total number of patients included in the study was 141

58 (41%) patients who had at least one episode of urinary tract infection

The number of male patients included in the study was110

The mean age in male cohort was 33.70±8.77 years

The number of female patients included in the study was 31

The mean age in the female cohort was 30.18±10.54 years

Recipient profile and urinary tract infection

Recipient	Urinary infection	No urinary infection
Male	41	69
Female	17	14

P-value 0.099

Urinary tract infection occurred in 37 % of male patients and 54% of female patients. The incidence of urinary infection in female recipients was more when compared to male recipients, which did not reach statistical significance.

The number of patients who received live related donor renal transplant was 100

The mean age of patients in this group was 30.35±9.42 years

The number of patients who received deceased donor renal transplant was 41

The mean age of patients in this group was 36.46±8.77 years

Donor profile and urinary tract infection

Donor	Urinary infection	No urinary infection
Live related donor	43	57
Deceased donor	15	26

P-value 0.57

Incidence of urinary infection in live donor transplant recipients was 43% and in deceased donor recipients was 37%. There is no significant difference in the incidence of urinary tract infection with regard to donor status.

Profile of organisms in relation to time of post transplant- ( )-female

Organism	<1month	2-6months	>6months
Candida	4 (1)	0	1 (1)
Klebsiella	11 (5)	8 (1)	11 (2)
E. coli	7 (1)	6 (1)	7 (6)
CONS	2	1	1
Enterococcus	1	1	1(1)
Acinetobacter	1	1 (1)	1
Proteus	0	1	0
Pseudomonas	1 (1)	0	2
Culture neg	1	2	0

Within bracket- number of females, CONS- Coagulase negative staphylococcus, Culture neg- Culture negative

The organism most commonly isolated was Klebsiella in 30 episodes of urinary tract infection, followed by E. coli in 20 episodes.

According to time of post transplant, in the 1st month Klebsiella urinary tract infection is more common in both males and females. In the 1 to 6months period post transplant and more than 6month post transplant also klebsiella urinary infection is more common in males. In females the common organism in the more than 6months post transplant is E. coli and in the 1 to 6 months post transplant there is equal occurrence of Klebsiella and E. coli urinary tract infection.

Among the gram positive organisms coagulase negative staphylococcus was isolated in three patients, Staphylococcus aureus in one, and Enterococcus species in three patients. The gram positive organism as a cause of urinary tract infection occured in 1st month, 1 to 6 months and more than 6 months post - transplant in male cohort with particularly Coagulase negative staphylococcus

The other gram negative organisms isolated include Acinetobacter in two patients, Proteus in one and Pseudomonas in three patients.

No organism could be identified in 3 patients with clinical features of urinary tract infection like pyuria, fever and tenderness over graft, which subsided with antibiotic treatment. Culture negative urinary tract infection occurred in 3episodes, with one episode of pyelonephritis of the graft, in allograft biopsy done in the early post transplant period for evaluation of graft dysfunction at 10th day post transplant.

Fungal urinary tract infection occurred in 5 patients, with 4 episodes occurring in less than 1 month post transplant. All the episodes of fungal urinary infections were due to Candida albicans. Three patients were treated with intravenous amphotericin for a total cumulative dose of 750mg.

One patient with Candida urinary infection was treated with oral Fluconazole for 2 weeks. One patient had fungal urinary infection after 2 year post transplant with failed allograft due to hyper delayed graft function in the early period, severe steroid resistant rejection requiring lymphocyte depleting agent with recurrent bacterial urinary tract infection.

Catheter days and urinary infection Catheterisation of bladder is a usual procedure in post renal transplant to favour healing of neo-cystourethrostomy. The relation between duration of catheterisation and the incidence of urinary tract infection is analysed

Catheter days	Urinary tract infection	No urinary tract infection
mean± S.D	9.69 ± 2.74	8 ± 1.79

P-valve >1

Mean number of catheter days with urinary tract infection was 9.69±2.74 days. The mean number of catheter days in those without urinary tract infection was

8±1.79 days. In subgroup analysis there is correlation of urinary infection with catheter days.

Catheter days	Urinary tract infection	Without urinary tract infection	Total number	Percent
< 7days	13	44	57	23%
7-10 days	25	33	58	47%
>10days	20	6	26	77%

P-value 0.00016

In patients with indwelling bladder catheterisation less than 7 days urinary infection occurred in 13 out of 57 patients. In patients with indwelling bladder catheterisation for 7 to 10 days, urinary tract infection occurred in 25 out of 58 patients. In those with indwelling catheterisation for more than 10 days urinary tract infection occurred in 20 out of 26 (75%) patients. There is a statistically significant correlation between the incidence urinary tract infection and the duration of indwelling bladder catheterisation

Stenting and urinary tract infection

50 patients out of 141 underwent prophylactic stenting in the study group. Mean number of days of stenting in those without urinary tract infection was 47.45±13.58. The mean number of days in those with urinary tract infection was 43.30±6.42. There is no significant correlation of duration of stenting in those with and in those without urinary tract infection. P value 0.21

Stenting and urinary tract infection

Stenting	Urinary tract infection	No urinary tract infection
Deceased donor	9	33
Live donor	5	3

P-value 0.03

In those patients who underwent prophylactic stenting 9 out of 42 patients in the deceased donor group had urinary tract infection.

In the live donor group, those who underwent prophylactic stenting 5 out of 8 recipients developed urinary tract infection.

There is a significant correlation with more of live related renal recipient with prophylactic stenting developing urinary tract infection.

Urinary infection and graft outcome

Serum creatinine in mg/dl	Urinary tract infection	Without urinary tract infection
Mean	1.718	1.484
Standard deviation	0.87	0.55

P-value 0.037

The mean serum Creatinine in those with urinary tract infection was 1.718 The mean serum Creatinine in those without urinary tract infection ws 1.484 There is a significant correlation of urinary tract infection with poor allograft outcome which is manifested as raised serum creatinine in those with urinary tract infection.

Delayed graft function and urinary tract infection

Graft function	Urinary tract infection	No urinary tract infection
Early graft function	48	75
Delayed graft function	10	8

P-value0.2044

Early graft function is defined as postoperative urine output more than 7000ml and serum creatinine normalised in 3 to 7 days.

Delayed graft function is defined as the need for dialysis in the first week in the absence of Hyperkalemia and when urinary obstruction, vascular occlusion or hyper acute rejection are ruled out as a cause for slow graft function. In the first 6 hours post-operatively, there will be rise in serum creatinine or urine output less than 300ml in the absence of volume depletion and adequate dose of diuretics. Serum Creatinine fall less than 25% from baseline in the first 24 hours and less than 10% fall from base line in 48 hours. When serum creatinine did not fall in the first 48 hours in the absence of rejection, delayed graft function is considered.

Urinary tract infection occurred in 10 of 18 patients with early graft function. Urinary infection occurred in 48 of 123 patients with delayed graft function. Even though a trend towards more urinary tract infection in those with delayed graft function, than in those with early graft function, there is no statistical significance.

Hepatitis C virus infection and UTI

Hepatitis C virus	Urinary tract infection	No urinary tract infection
HCV infection	18	10
No HCV infection	40	73

P-value 0.0091

Urinary tract infection occurred in 18 out of 28 patients with hepatitis C co-infection. Urinary tract infection occurred in 40 out of 114 patients without

hepatitis C infection. There is a strong significant correlation with hepatitis C co-infection and urinary tract infection in the post transplant period.

Diabetes mellitus and urinary tract infection

Diabetic status	Urinary tract infection	No urinary tract infection
Diabetes mellitus	18(1)	25(5)
Non-diabetic	40	58

P–value 1.00

Urinary tract infection occurred in 18 out of 43 patients with diabetes mellitus. Urinary tract infection occurred in 40 out of 98 patients in those without diabetes. Diabetes mellitus was noted in 43 out of 141 patients. Pre transplant diabetes mellitus was noted in 5 patients in those with urinary tract infection. New-onset diabetes post transplant was noted in 20 patients without urinary tract infection and 17 patients with urinary tract infection.

There is no statistically significant correlation of the incidence urinary tract infection in those with diabetes mellitus and in those without urinary infection

Acute rejection episodes and urinary tract infection

Rejection	Urinary tract infection	No urinary tract infection
Acute rejection/anti-rejection therapy	16	29(5)
N o anti-rejection therapy	42	54

P-value 0.463

Empirical antirejection therapy was administered in 5 patients, in those without urinary tract infection group.

Urinary tract infection occurred in 16 out of 45 patients, who received anti-rejection therapy. Urinary tract infection occurred in 42 out of 96 patients, who never received ART.

There is no significant correlation with anti rejection therapy and the occurrence of urinary tract infection in renal transplant recipient.

Cytomegalovirus infection and urinary tract infection

Cytomegalovirus	Urinary tract infection	No urinary tract infection
CMV disease	7	8
No CMV disease	51	75

P-value 0.7828

Urinary tract infection occurred in 7 out of 15 patients who had cytomegaloviral disease. There is no correlation with cytomegalovirus disease and the occurrence of urinary tract infection in transplant recipient

Structural abnormalities

Structural lesions	Age/Sex	organism	Time of occurrence	Number of episodes	comorbidities
Ureteric stricture	26M	Klebsiella oxytoca	11month	1	HCV infection/ ART
Ureteric stricture with VUR	21M	Klebsiella oxytoca	4^{th} day, 10^{th} month, 12^{th} month	3	Anti-rejection therapy (ART)
Meatal stenosis	20M	Culture negative	3^{rd} month	1	HCV infection
PUJ obstruction	45M	E. coli	1year 5month	1	NODAT
Scar in the kidney	34F	E. coli	6year	1	HCV infection
Neurogenic bladder	35 M	Klebsiella oxytoca	2month onwards	6	CMV infection
Horse shoe kidney	22M	No		0	Anti-rejection
VUR	30M	No		0	

Pretransplant structural abnormalities were identified in 7patients and neurogenic bladder dysfunction due to spinal injury was present in one patient.

Three patients had bladder outlet obstruction, one had meatal stenosis and other two patients had ureteric stricture.

Isolated vesicoureteric reflux, horse shoe kidney, scar in the allograft and pelvi-ureteric junction obstruction -each present in one patient.

Three patients had urinary tract infection in the 1 to 6 month period. Three patients present with urinary tract infection in the late post transplant period.

Acute rejection occurred in 3 out of 7 patients with structural abnormalities, with two patients with stricture urethra having late rejection.

Among them, one patient had transplant ureteric stricture in the 11^{th} post transplant month. He received live related transplant with father as donor, on triple immunosuppression with tacrolimus, mycophenolate mofetil and Prednisolone. He had chicken pox in the 8^{th} post transplant month. He had gradual worsening renal failure, with gross hydroureteronephrosis of transplant kidney, requiring dialysis. He initially underwent percutaneous nephrostomy, followed by pyeloureteroplasty. He developed klebsiella urinary tract infection after 3 weeks of procedure.

Graft pyelonephritis

No	Age/sex	NODAT	HCV	Rejection	Outcome	Co-morbidity
1	56F	Yes	No	No	3.1-1.0mg	Stenting45days
2	23M	No	No	No	3.5-2.4mg	Stenting56days
3	27M	No	No	Yes steroid 2.5gm	Dialysis dependent	
4	26M	Yes	Yes	No	2.5-1.6mg	Transplant ureteric stricture.stent21days

Four patients presented with low grade fever and graft dysfunction. All of them underwent allograft biopsy for graft dysfunction. All patients had no urinary symptoms in the form of dysuria, frequency and pain or tenderness over the graft. One patient had transplant ureteric stricture, for which he underwent pyeloureteroplasty to native ureter with double J stenting. The stent was removed after three weeks after that he presented with graft dysfunction and diabetic ketoacidosis. One patient with pyelonephritis in the allograft biopsy received steroids 2.5gms in the previous week for acute cellular rejection, masking the symptoms of UTI. Diabetes was present in two of the patients. Stenting was done in 3 out of four patients. All of those with stenting developed urinary tract infection immediately after stent removal. Two patients had recovery of renal function following treatment of urinary tract infection.

One patient had partial recovery of renal function. One patient gradually progressed to end stage renal disease over a period of 5months.

Renal abscess

No	Age /sex	HepatitisC	Sr creatinine	organism	duration	Outcome
1	37/M	Yes	1.8mg	pseudomonas	1yr 10 month	Per-cutaneous drainage
2	24/F	CMV twice	1.6mg	E. coli	2yr 4month	Per-cutaneous drainage

Renal abscess occurred on the late post transplant period, more than 18 month post transplant. The serum creatinine at the time of abscess formation was 1.8mg and 1.6mg respectively in the two patients.

Recurrent urinary tract infection

Recurrent UTI is defined as occurrence of more three episodes per year. Out of 58 patients with urinary tract infection, six patients had recurrent episodes of infection.

S.No	Age/sex	No of episodes	donor	NODAT	HCV	Anti-rejection	DGF	Stent duration	0ther co-morbidities
1	47M	4 E. coli	live	Yes	Yes	Yes/late	No	No	FSGS recurrence
2	24M	7 kleb	live	Yes	Yes	No	No	No	Hepatitis
3	43M	5 kleb	cadaver	Yes	No	No	Yes	42days	Expanded donor
4	41m	3 kleb	cadaver	Yes	Yes	Yes/late	Yes	42days	Hepatitis
5	35M	6 kleb	live	No	No	No	No	42days	CMV/ neurogenic bladder
6	22M	3 kleb	cadaver	No	No	No	No	42days	IgA recurrence

Kleb-klebsiella, cadaver- deceased, FSGS-focal segmental glomerulosclerosis, IgA-immunoglobulin A, CMV-cytomegalovirus, NODAT-new onset diabetes after transplant

The organism most commonly isolated in those with recurrent UTI was klebsiella oxytoca, and in one patient E. coli.

One out of 6 received induction therapy in the form of 2 doses of basiliximab. All the patients were on triple immunosuppression, with three on tacrolimus, MMF and steroid, and other three on cyclosporine, Azathioprine and steroid.

NODAT was noted in 4 out of 6 patients with recurrent urinary tract infection.

HCV infection occurred in 3 out of 6 patients with recurrent urinary tract infection; two of them had active hepatitis with worsening liver function also.

Rejection episodes occurred in 2 out of 6 patients, with both patient developing late rejection after multiple episodes of urinary tract infection.

Recurrence of disease (FSGS/IgA nephropathy) occurred in 2 out of 6 patients, with proteinuria occurring from third post transplant month.

DISCUSSION

Infection is a common complication in the renal transplant recipient. In the initial months of post transplant period bacterial infection is more common, with urinary tract infection occurring as a common infection among bacterial infections.

According to Hussain et al the incidence of urinary tract infection was 46%[69]. The incidence of urinary infection in our cohort was 41%. The reported frequency varies in various studies ranging from 18% to 79%.

According to Roberto Rivera-Sanchez et al et al, E. coli was the most common organism 31%, followed by candida albicans 21% and enterococcus species 10%[19]. In our study klebsiella species is the most common organism isolated followed by E.coli. Among gram positive organism coagulase negative staphylococcus urinary tract infection is more common.

According to Lyrova et al there is no significant difference in graft function and allograft survival in those who have developed urinary tract infection during a follow-up of 5 years[87]. According to Pelle et al there is a poor long term outcome in those with acute graft pyelonephritis, documented by a lower creatinine clearance by 50% in those with post transplant UTI, when compared to those without urinary tract infection over 4 years follow up[24].

In our cohort also there is a significantly worse graft outcome in the form of raised creatinine in those with urinary infection when compared to those who never had urinary tract infection.

According to Kamath et al there is a correlation with pre transplant glomerular disease and urinary infection[1]. According to the author the pre transplant immunosuppression, by increasing the net immunosuppression post transplant predisposes to urinary infection. In our cohort there is increased incidence of urinary infection in those with proteinuria due to recurrent glomerular disease with two patients presenting as recurrent urinary tract infection, even though they received no immunosuppression during the pre transplant period.

According to Magali Gril et al there is more incidence of graft pyelonephritis in female recipient[86]. In our study also there is increased incidence of urinary tract infection in female recipient, which did not reach statistical significance. The increased incidence of urinary infection in female may be due to anatomic factors like shorter female urethra and proximity of the vagina and urethra to the anal canal favouring colonization[49].

There is no correlation between diabetes, cytomegalovirus infection and rejection episodes with the increased incidence of urinary tract infection as shown in various study[17].

The incidence of urinary tract infection is more common in those with hepatitis C co-infection. Hepatitis C virus is an immunomodulating virus like cytomegalovirus and predispose to more risk of infections.

According to David Roth et al the risk of infection is considered as a function of time line, initial 6months and more than 6 months[80]. In the initial 6months the morbidity and mortality due to all infections in the post transplant patient with HCV infection is increased by a factor of 2.51.

The infection risk is not increased in the late post transplant period. But, the risk for cardiovascular mortality is decreased significantly in post transplants irrespective of the time since transplantation.

When, the mortality due to infection alone is considered, it is increased by a factor of 26 fold, in post transplant when compared to pre transplant. In our study, in univariate analysis there is significantly increased risk of urinary tract infection in the post transplant, with hepatitis C co-infection.

Three patients with HCV co-infection post transplant presented with recurrent urinary infection[72]. Two patients developed jaundice with active hepatitis after repeated urinary tract infection, associated with worsening allograft function and succumbed to the illness. Among them one was asymptomatic for HCV pretransplant, with hepatitis C antibody negative and mild elevation of liver enzymes, and nucleic acid test was not done pre-transplant for him[74]. He was on triple immunosuppression including

Azathioprine, which would have worsened his hepatitis. The pre- transplant diagnosis of hepatitis C virus status using nucleic acid based testing[22] might have been useful in choosing the non Azathioprine containing immunosuppression and optimization of immunosuppression, so that over immunosuppression can be avoided, which may be helpful in reducing infection related death including urinary tract infection and progression of liver disease[21].

According to Tanweer Iqbql study there is a significant correlation between the number of catheter days and urinary tract infection, with more urinary tract infection whenever the catheter was retained for prolonged periods[66]**.** In our study also there is a strong linear correlation with the number of days of catheterisation and occurrence of urinary tract infection. In patients, in whom the catheter was retained for less than 7days, 23% developed urinary tract infection. In those patients in whom the catheter was retained for 7 to 10 days, 47% developed urinary tract infection. When catheter was retained for more than 10 days, about 77% of patients developed urinary tract infection in the post transplant period.

Urinary catheterisation was done by the urologist in the immediate post-transplant period and continuous bladder drainage was being maintained to avoid the early urological complication like urine leak. Whenever the drain volume was more than 30 ml operating surgeon in doubt of urological

complication, retain the bladder catheter for some more days. With every additional day of catheterisation, there is progressive increase in the percentage of patients developing colonization of the urinary tract, which commonly arise trough the peri-urethral route[20].

With longer duration of catheterisation there is every chance of biofilm formation with the organism secreted substances and host factors, forming a protective barrier to the organism from the host immunological mechanism and administered antimicrobial substances, and multiple organisms in the colony of biofilm exchange genetic material between organisms including multidrug resistant plasmid.

The organism causing urinary tract infection in those with indwelling catheterisation frequently originate from the hospital environment, and due to biofilm formation have resistant to multiple antimicrobials[20].

The surgeon should balance the risk of urological complication from early catheter removal which compromise the neo-ureterocystostomy and the risk of urinary catheterisation from retaining the catheter for a long period.

The anastomosis done in the renal transplant surgery between donor ureter and the recipient bladder is different from the other urological neo-ureterocystostomy[29].

In routine urological procedure the diseased ureter is anastomosed to the diseased bladder making the anastomosis at risk of compromise when it is not supported by continuous bladder drainage[30].

In the renal transplant surgery the anastomosis made between the healthy donor ureter and usually healthy recipient ureter making the risk of anastomosis complication less likely, so that early removal of catheter can reduce the incidence of catheter associated urinary tract infection in the profoundly immunosuppressed recipient in the early post transplant period.

In the same study the author compares the incidence of urinary tract infection in those with stenting and those without stenting. There is no increased incidence of urinary tract infection in in those with stenting when compared to those without stenting[26].

In our study about 50 patients underwent prophylactic stenting. There is no significant difference in the duration of stent placement between those with urinary tract infection, with those without urinary tract infection. Most of our patient develops urinary tract infection within a week of stent placement, even though some may develop infection during stent insitu.

Stenting is the procedure done to avoid early urological complication in the post transplant patient. Stenting decrease the incidence of urine leak, ureteric stricture and kinking of the ureter which are the complication arising from neo ureterocystostomy.

By creating tension free water tight ureterocystostomy anastomosis and preserving the vascular supply of the ureter by preserving the golden triangle and by avoiding any dissection, the early urological complications can largely be avoided.

Stenting predisposes not only to urinary tract infection and also to the formation of biofilm on the surface similar to that occurring in bladder catheterisation, predisposing formation of multi drug resistant organism. There is also increased incidence of late urinary stricture in those with prophylactic stenting.

In our study stent was kept for an average more than 6weeks. And there is also more urinary tract infection in live-related transplant when compared to deceased donor transplant with urinary stenting[27]. This may be due to the fact, in deceased donor transplant routine prophylactic stenting is being followed, since there is prolonged ischemic time and there is every chance for no urine output after clamp release, so ensuring water tight anastomosis may not be possible.

In live donor transplant, the indication for stenting may be abnormal bladder[27], which may be risk factor for urinary tract infection by itself, and our study population with stenting in live related transplant is too small to make any comment regarding increased urinary infection in those with stenting.

If at all stenting is done for avoiding early urological complication, it should be removed as early as possible preferably with in 3 to 4 weeks, to decrease the incidence of urinary tract infection. As most of the infections in the stented patients occur immediately after removal of stent, there should be close surveillance for urinary tract infection in the early stent removal period, so that any infection can be brought under control early.

Renal abscess occurred in two patients in our study. The occurrence of infection is due to infection with immunomodulatory viruses predisposing to bacterial infections.

Patients may have few signs or symptoms of infection because of their immunosuppressed state. They may present with fever of unknown origin, pain, or symptoms related to the pressure of the abscess on the transplanted system. Peri-transplant abscesses usually develop within the first few weeks after transplantation. Abscess is usually caused by infection of peri-nephric collection or from complication of pyelonephritis. Abscesses may be treated with either ultra sound or CT-guided percutaneous drainage. Both intrarenal and extrarenal abscesses usually respond to percutaneous drainage and systemic antibiotics. In our patient the late occurrence of renal abscess complicating urinary tract infection is due to both of them having immunomodulatory viral infection, hepatitis C virus in one and recurrent cytomegalovirus in the other patient. Both patient underwent imaging guided

percutaneous aspiration, but had progressive worsening of the disease and succumbed to the illness[88].

One patient presented with E. coli urinary tract infection with renal abscess 2year 4months post transplant. She was on triple immunosuppression based on cyclosporine, Azathioprine and steroid. She had three episodes of cytomegalovirus infection. The other presented with pseudomonas urinary tract infection with psoas abscess 18 months post transplant. He was diagnosed to have HCV co-infection after transplant, and he was also on triple immunosuppression based on cyclosporine, Azathioprine and steroid. Cytomegalovirus infection causes immunomodulation by three mechanisms 1.Cytomegalovirus reduces cell surface expression of major histocompatibility complex class I antigen on the surface of cells impairing T-cell recoganization. 2. Cytomegalovirus produces IL-10 which inhibits proliferation and cytokine production by mononuclear cells. It also inhibits maturation and induces apoptosis of dentritic cells. 3. Cytomegalovirus causes suppression of antigen specific cytotoxic T lymphocyte function and cause a decrease in CD4+ cell function leading to global impairment of cell-mediated immunity.

In this manner it predisposes the patient to bacterial, fungal and parasitic infection. The indirect effects of cytomegalovirus are rejection and predisposition to opportunistic infection, causing decreased patient and graft survival[17].

Polyoma virus nephropathy presenting as transplant ureteric stricture occurred in one patient, and he was on triple immunosuppression with tacrolimus, mycophenolate mofetil and steroid. He presented with ureteric stricture in the 8th post transplant month which is the usual presenting time of polyomavirus nephropathy reactivation. Polyoma virus usually manifests in the 6 to 18 month post transplant. Prosser et al used enzyme-linked immunosorbent spot assay to measure the cellular immunity in those with polyomavirus infection by analysing interferon gamma levels[85]. He demonstrated a fourfold rise in titre of interferon gamma levels with resolution of infection. This shows that the impact of intact cell-mediated immunity in the prevention of polyomavirus reactivation and why it occurs more commonly in those on potent immunosuppression tacrolimus when compared to cyclosporine. According to Aoron Dall et al polyoma virus infection are usually asymptomatic and polyoma viral infection occasionally present as stricture of transplant ureter[84].

Awadalla et al showed, an increased HLA mismatches with occurrence of nephropathy, implying allo-immunisation as a potentiating factor for polyoma virus infection reactivation[83]. BK virus reactivation is rarely seen in those who have undergone non renal solid organ transplantation. The patient will usually be on triple drug including tacrolimus. The disease should be managed with reduction in antiproliferative drug, or temporary withdrawal of the drug, which result in gradual reduction in viral load over 12 weeks. Some

may also need the reduction of calcineurin inhibitor to achieve maximum therapeutic response. Acute rejection can occur in about 10% of the patient during tapering of immunosuppression, which should be actively sought during reduction of immunosuppression.

In our cohort there is no case of documented adenovirus infection. One patient presented with hematuria and graft dysfunction. He underwent renal biopsy in the 30th post transplant day diagnosed as acute cellular rejection, and he was treated with anti rejection therapy. He had very high cyclosporine level, and developed fever and expired in the 2nd month post transplant. He might have suffered from adenovirus infection, since we have not tested him for adenovirus by PCR.

Adenovirus usually present in the early post transplant period with short history of hematuria, fever and biopsy showing interstitial mononuclear infiltrates[81]. The early recognition of this infection is needed, since it respond to low dose of single dose cidofovir with rapid recovery of renal function, even in those with dialysis requiring renal failure[82].

Another patient in our cohort presented with hemorrhagic cystitis in the second post transplant month. He developed cytomegalovirus and klebsiella urinary tract infection in the 4th month post transplant. This shows that cytomegalovirus can also present as hemorrhagic cystitis.

When patient presents with hematuria, they should be screened for adenovirus, cytomegalovirus and polyoma virus according to the time period in the post transplant setting.

CONCLUSIONS

1. Urinary tract infection is a common infection in renal transplant recipients.

2. Klebsiella species is the commonest organism causing urinary tract infection in this study.

3. There is no correlation with cytomegalovirus disease, pre existing diabetes, NODAT (New Onset Diabetes After Transplantation) and anti rejection therapy on the occurrence of urinary tract infection.

4. The incidence of urinary tract infection is increased in those with hepatitis C virus coinfection.

5. Urinary infection is increased as a function of number of days of indwelling urethral catheterization post transplant, with more incidence of urinary tract infection with increased number of catheter days.

6. The incidence of urinary tract infection is not increased in those with prophylactic stenting.

7. Urinary tract infection in the renal transplant recipients is associated with poor long term graft function

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